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Using a Transmission Dynamic Model of Rotavirus Infection to Determine the Cost-Effectiveness of Rotavirus Vaccination in Bangladesh

By

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**Thesis submitted to the Department of Microbial Disease Epidemiology at
Yale School of Public Health in partial fulfillment of the requirements
of the degree of Master of Public Health**

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RESEARCH ABSTRACT

INTRODUCTION: Rotavirus is the leading cause of severe gastroenteritis worldwide. Due to the morbidity and mortality of the disease, introduction of rotavirus vaccination in routine childhood immunization programs is recommended for all nations by the World Health Organization.

OBJECTIVE: The primary objective of this study was to assess the cost-effectiveness of rotavirus vaccine introduction in Bangladesh from 2015 to 2024.

METHODS: We used a compartmental SIRS-like model developed by Pitzer *et al* (2009) to simulate health outcomes due to rotavirus infection in Bangladesh under two scenarios: 92% vaccination coverage and no vaccination (Pitzer et al., 2009). The model was first fitted to data on age-specific rotavirus hospitalizations at the *International Center for Diarrheal Disease Research, Bangladesh* (icddr,b) hospital in Dhaka to estimate transmission parameters such as R_0 , and then scaled to the entire country by refitting to estimates of rotavirus disease burden for Bangladesh. We calculated medical costs associated with each health outcome and determined the cost of introducing the rotavirus vaccine. We used these estimates to develop an Excel model that examined the incremental cost effectiveness, from the health care system perspective, of introducing rotavirus vaccine into Bangladesh's National Immunization Program. The outcome measure selected was discounted (3%) US\$ per Disability Adjusted Life Year (DALY) averted, in children under five.

RESULTS: According to our model, vaccine introduction would prevent ~49,000 deaths over ten years. Under vaccination, 10.2 million discounted DALYs would be averted, and \$25.7 million in discounted costs of treating rotavirus infection would be saved; the total discounted cost of vaccine introduction would be \$550 million. The incremental cost per DALY saved was \$51.19, and varied from \$6.80 to \$78.0 per DALY averted when conducting one-way sensitivity analyses of model variables. The variables that had the biggest impact on the cost per DALY were vaccine efficacy, vaccine price and annual number of rotavirus episodes.

CONCLUSION: Judged by the WHO's widely-accepted standards, introduction of rotavirus vaccination to Bangladesh is very cost-effective and would likely be instrumental in decreasing morbidity and mortality caused by rotavirus in children under five.

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INTRODUCTION

Rotavirus is the leading cause of severe gastroenteritis worldwide and, in 2008, was estimated to result in 420,000 to 494,000 deaths in children <5 years old (Tate et al., 2012) (Glass, Parashar, Patel, Gentsch, & Jiang, 2014; Parashar et al., 2009). This disease imposes a particularly heavy burden on health systems in developing countries, where 95% of deaths due to rotavirus occur (Parashar, Hummelman, Bresee, Miller, & Glass, 2003). Due to the morbidity and mortality of this disease, introduction of rotavirus vaccination in routine childhood immunization programs is recommended for all nations by the World Health Organization (WHO), especially for countries with a high incidence of severe rotavirus gastroenteritis (World Health Organization, 2013). There are two vaccines widely available (Rotarix and RotaTeq) and a third (Rotavac) has recently passed phase III Clinical Trials (Tate et al., 2014). In spite of this recommendation and the fact that vaccines have been licensed for use in over 100 countries, many nations have yet to introduce rotavirus vaccination into their immunization schedules (Glass et al., 2014). Lack of information on disease burden, cost of expanding cold chain equipment and knowledge of the impact of vaccination in the specific context, coupled with funding gaps, make it difficult for key decision-makers to promote the introduction of new vaccines (Uddin, Sarma, Bari, & Koehlmoos, 2013). Cost effectiveness analyses could help weigh the costs and benefits of vaccine introduction, and in this way speed the decision process.

An estimated 5,600 to 9,400 annual deaths due to rotavirus gastroenteritis occur in Bangladesh, accounting for approximately 2% of all deaths from this disease worldwide (Tanaka et al., 2007; Tate et al., 2012). In spite of this dramatic death toll, information about the epidemiology and burden of rotavirus infection in Bangladesh is still limited. One of the few studies available estimated that the population-based incidence of hospitalization due to rotavirus was 10.8 to 19.6 per 1000 children under five years of age in a rural region of Bangladesh (Zaman et al., 2009).

Because of rotavirus morbidity and mortality, vaccination in Bangladesh should be considered. Although there have been previous studies measuring the cost-effectiveness of rotavirus vaccines in low socio economic settings, none have been conducted for Bangladesh. For example, Rheingans *et al* (2009) estimated a cost of \$88 per DALY averted for low income countries, with a vaccine price of \$5.00; while Atherly *et al* (2009) estimated a cost of \$43 per DALY averted for developing countries, with a vaccine price that decreased from \$7.00 to \$1.25 over 19 years (Atherly et al., 2009; Rheingans et al., 2009). Low-income countries have limited monetary resources to allocate to vaccination, and having robust cost-effectiveness analysis, like the ones mentioned above, is crucial in their decision process. To help inform this decision in Bangladesh, we developed a cost-effectiveness analysis of rotavirus vaccination using a dynamic model of rotavirus infection for the country, which takes into account both the direct and indirect protection from vaccination. This, it is hoped, will help inform the decision of whether or not to introduce rotavirus vaccination.

METHODS

Overview

We used a transmission dynamic model developed by Pitzer, *et al* (2009) to estimate health outcomes due to rotavirus infection in Bangladesh, under two scenarios: 92% vaccination coverage and no vaccination (Pitzer et al., 2009). We calculated medical costs associated with each health outcome and determined the cost of rotavirus vaccine introduction. We used these estimates to develop an Excel model that examined the incremental cost effectiveness, from the health care system perspective, of introducing rotavirus vaccination into Bangladesh's National Immunization Program. The outcome measure selected for the cost-effectiveness analysis was US\$ per Disability Adjusted Life Years (DALYs) averted in children under five. In accordance with accepted practice (Gold, Siegel, Russell, & Weinstein, 1996), all healthcare costs and vaccine introduction costs were converted to 2014 US dollars using the US Consumer Price Index (Bureau of Labor Statistics, 2015; Hayford, Uddin, Koehlmoos, & Bishai, 2014). When used to perform the cost-effectiveness analysis, all costs and benefits were discounted at an annual rate of 3% discount (Gold et al., 1996).

Transmission dynamic model

Dynamic model description. We used a compartmental SIRS-like model developed by Pitzer *et al* (2009) to simulate the dynamics of rotavirus infection in Bangladesh. This model reflects an increase in incomplete immunity following each subsequent infection, as rotavirus is an imperfectly immunizing infection. In this model, children are born into the first compartment, where they have immunity provided by maternal antibodies (M). After 6 months (on average), immunity wanes and they become susceptible to infection (S_0). They get infected at a rate of infection λ_1 and transition to the primary rotavirus infection compartment (I_1). Infected individuals recover at a rate γ_1 and enter the recovered state (R_1) in which they are temporarily immune. Immunity wanes and individuals become susceptible again (S_1) and get infected at a reduced infection rate (λ_2). Infected individuals transition into the secondary rotavirus infection state (I_2). Once they recover, at a faster rate (γ_2), they enter the second recovered compartment (R_2). With time individuals become susceptible once more (S_2), but have partial immunity. The model assumes that individuals in this S_2 state can get re-infected but that in all subsequent infections (I_A), they will be asymptomatic or mildly symptomatic (see Figure 1.A) (Pitzer et al., 2009). The probability of developing severe diarrhea given infection was based on a study conducted by Gladstone *et al* (2011) in which a cohort of children in India was followed for three years after birth to determine rotavirus infection (based on seroconversion and detection of rotavirus in stool) and development of RVGE (Gladstone et al., 2011). We based our estimates on Gladstone *et al* (2011) because we believe data from India better reflect disease development in Bangladesh, especially when compared to other studies that looked at the association between infection and the development of rotavirus immunity in regions of the world with different social economic realities, such as Mexico (Lopman et al., 2012; Velazquez et al., 1996).

Table 1. Fixed parameter values for the transmission dynamic model

Parameter	Value	Source
Duration of maternal immunity	6 months (gamma-distributed)	(Pitzer et al., 2011)
Duration of infectiousness		
First infection	7 days	(Pitzer et al., 2012)
Second infection	3.5 days	
Relative risk of infection following		
First infection	0.62	(Gladstone et al., 2011; Velazquez et al., 1996)
Second infection	0.35	(Gladstone et al., 2011; Velazquez et al., 1996)
Proportion of Infections with any RVGE (severe RVGE)		
First infection	0.41 (0.063)	(Gladstone et al., 2011)
Second infection	0.35 (0.077)	(Gladstone et al., 2011)
Subsequent infections	0.21 (0.00023)	(Gladstone et al., 2011), estimated
Relative infectiousness of secondary infection	0.5	Assumption, (Koopman, Monto, & Longini, 1989)

Dynamic model fitting. To estimate transmission parameters, such as the basic reproduction number (R_0), the duration of immunity following infection, and the proportion of subsequent infections (following two infections) that are severe, we fitted the model to data on age-specific rotavirus hospitalizations at the *International Center for Diarrheal Disease Research, Bangladesh (icddr,b)* hospital in Dhaka. The surveillance system at *icddr,b* has been described previously (Stoll et al., 1982; Tanaka et al., 2007). We had weekly data on patients who tested positive for rotavirus from January 1990 to December 2012. When this data was collected, rotavirus vaccination was not part of the national immunization program. The population was divided into 17 age categories (less than 1 month, 1 month, 2 month, 3 month, 4 month, 5 month, 6 month, 7 month, 8 month, 9 month, 10 month, 11 month, 1 year, 2 years, 3 years, 4 years, ≥ 5 years); for the purposes of our analysis, we only fit the model to data on patients <5 years old. We assumed homogeneous mixing; all individuals had an equal probability of contacting other individuals irrespective of age (Pitzer et al., 2009). We fit the model to the data by maximum likelihood estimation, using a log-likelihood function that assumes the observed cases are Poisson-distributed with the rate parameter equal to the simulation-based prediction of weekly cases in each age-group:

$$LL_{i,t} = -hD_{i,t} + H_{i,t} \ln(hD_{i,t}) - \sum_{j=1}^{H_{i,t}} \ln j$$

$$LL = \sum_t \sum_{i=1}^{16} LL_{i,t}$$

where $D_{i,t}$ is the number of severe rotavirus-related diarrhea cases in each age class i at a time t , h is the proportion of severe diarrhea cases that are hospitalized, and $H_{i,t}$ is the number of hospitalized diarrhea cases in each age class i at a time t .

When simulating the model, we initiated the model with one infectious individual in each age group and discarded a burn-in period of 40 years, which we determined (by visual inspection) was enough time to reach equilibrium.

Model scaling and re-fitting. We scaled the model to all of Bangladesh using the following fixed estimates obtained from the initial fitting of the model: R_0 , *duration of immunity*, and *proportion of subsequent infections that are severe*. Scaling allowed the model to simulate the total number of any RVGE and severe RVGE cases for the country. In order to simulate the number of mild cases, outpatient visits, hospitalizations and deaths from the model output (total number of RVGE and severe RVGE cases), we re-fitted the model to obtain reporting fractions. We determined a reporting fraction of mild cases to total number of cases, and outpatient visits to mild cases. We also determined a reporting fraction for hospitalizations to severe RVGE and deaths to hospitalizations. In order to obtain the reporting fractions we used estimates, calculated from literature, of the number of hospitalizations, outpatient visits, episodes and deaths due to rotavirus infection per year in Bangladesh.

Estimates of yearly number of hospitalizations, outpatient visits, and episodes due to rotavirus infection were based on published data from Zaman *et al* (2009) and John *et al* (2014). Zaman *et al* (2009) reported an overall risk of hospitalization due to rotavirus infection of 16.4 for every 1000 children under the age of five in Bangladesh (Zaman *et al.*, 2009). In this study, the highest risk of hospitalization observed in a year, during the six-year study, was 19.7 for every 1000 children and the lowest risk was 10.8 for every 1000 children. These risks were used as the upper and lower bound for the risk of hospitalization in Bangladesh, and the overall estimate was considered the best guess. The risks were then multiplied by the annual under-five population for the country to obtain the total number of hospitalizations during a year. We assumed hospitalizations would be normally distributed with the lower and upper bound estimates representing the 95% confidence interval (Briggs, Sculpher, & Claxton, 2006).

To determine the number of outpatient visits and cases per year, we used estimates of rotavirus disease burden from India and adapted them to Bangladesh. John *et al* (2014) estimated a ratio of 3.75 outpatient visits for each hospitalization and 13.03 episodes of rotavirus per hospitalization in India (John *et al.*, 2014). To obtain the total annual number of outpatient visits and rotavirus episodes in Bangladesh, we multiplied the number of hospitalizations per year and its 95% confidence interval by the ratio of outpatient visits to hospitalizations and the ratio of episodes to hospitalization. Finally, we used estimates of rotavirus mortality in Bangladesh published by Tate, *et al* (2012) for the number of deaths per year, and assumed that deaths would be log-normally distributed. Tate, *et al* (2012) reports mortality due to rotavirus to be between 50 and 100 deaths per 100,000 children under five; we assumed this range corresponded to the 95% confidence interval.

Table 2. Input variables used to scale up the model to reflect rotavirus disease burden in Bangladesh

Variable	Best estimate (95% confidence interval)	Distribution
Health variables		
Rotavirus episodes per year (million)	3.213 (2.139-3.906)	Normal
Rotavirus outpatient visits per year (million)	0.924 (0.615-1.123)	Normal
Rotavirus hospitalizations per year (million)	0.246 (0.164-0.299)	Normal
Rotavirus deaths per year ^a	9,857 (7,607-15,213)	Log normal

^a Estimate was taken from (Tate et al., 2012)

We fitted the model to these data by simulating the model, then using a Markov Chain Monte Carlo (MCMC) with a Metro-Hastings algorithm to sample from the posterior distribution of the reporting fractions for the ratio of episodes to any RVGE, ratio of outpatient visits to episodes, ratio of hospitalizations to severe RVGE, and ratio of deaths to hospitalizations. We generated two chains of 100,000 samples from the posterior distribution after an initial burn-in of 10,000 iterations, then thinned the chains by sampling every 10th iteration.

Using the modified model. The model, after fitting and scaling, was used to simulate rotavirus transmission in Bangladesh from 2015 to 2024 under two scenarios: no vaccine and vaccine introduction. Under the second scenario the model assumed that 53% of children vaccinated would seroconvert following a full course of 2 doses (Patel et al., 2013). This assumption is based on Patel et al, (2013) where the IgA antibody titer was taken as a marker of vaccine efficacy. Based on this, the model assumed that each dose of vaccine provided immunity equal to that obtained after a single natural infection, given seroconversion took place. Immunity after two natural infections, and therefore vaccination according to our model, provides some protection against subsequent infections and carriage, and a slightly stronger protection against development of symptoms given infection. Because we estimated that the risk of severe RVGE was minimal after second infections, the modeled vaccine efficacy against severe RVGE is approximately equal to the proportion of children who seroconvert (Patel et al., 2013).

Table 3. Input variables used in the vaccination scenario

Variable	Best estimate (Range)	Reference
Vaccine efficacy	0.53 (0.41, 0.64)	(Patel et al., 2013)
Vaccine coverage	0.92 (0.80, 1.00)	(GAVI the vaccine alliance, 2015e)

Vaccine coverage. Vaccine coverage was set at 92%, based on the 2013 vaccine coverage for the third dose of Diphtheria-Tetanus-Pertussis vaccine (DTP3) in Bangladesh (GAVI the vaccine alliance, 2015e). It is reasonable to assume that similar coverage levels to those for DTP3 could be achieved because rotavirus vaccine would form part of the national immunization program, and be administered concomitantly with the first and second dose of DTP vaccine. To be conservative, we chose to set coverage at the level of DTP3 and not DTP2, which would be higher. We assumed that every child

vaccinated would receive the full vaccine course of two doses. We assumed the first dose was administered at 2 months of age and the second dose was administered at 4 months of age.

Direct versus indirect effect of vaccination. To quantify the potential benefit of herd immunity, we estimated the difference in number of hospitalizations under the population direct versus overall effect of vaccination. We took into account the vaccine efficacy and vaccine coverage over time to determine the number of hospitalizations predicted under population direct effect of vaccination (Pitzer et al., 2012).

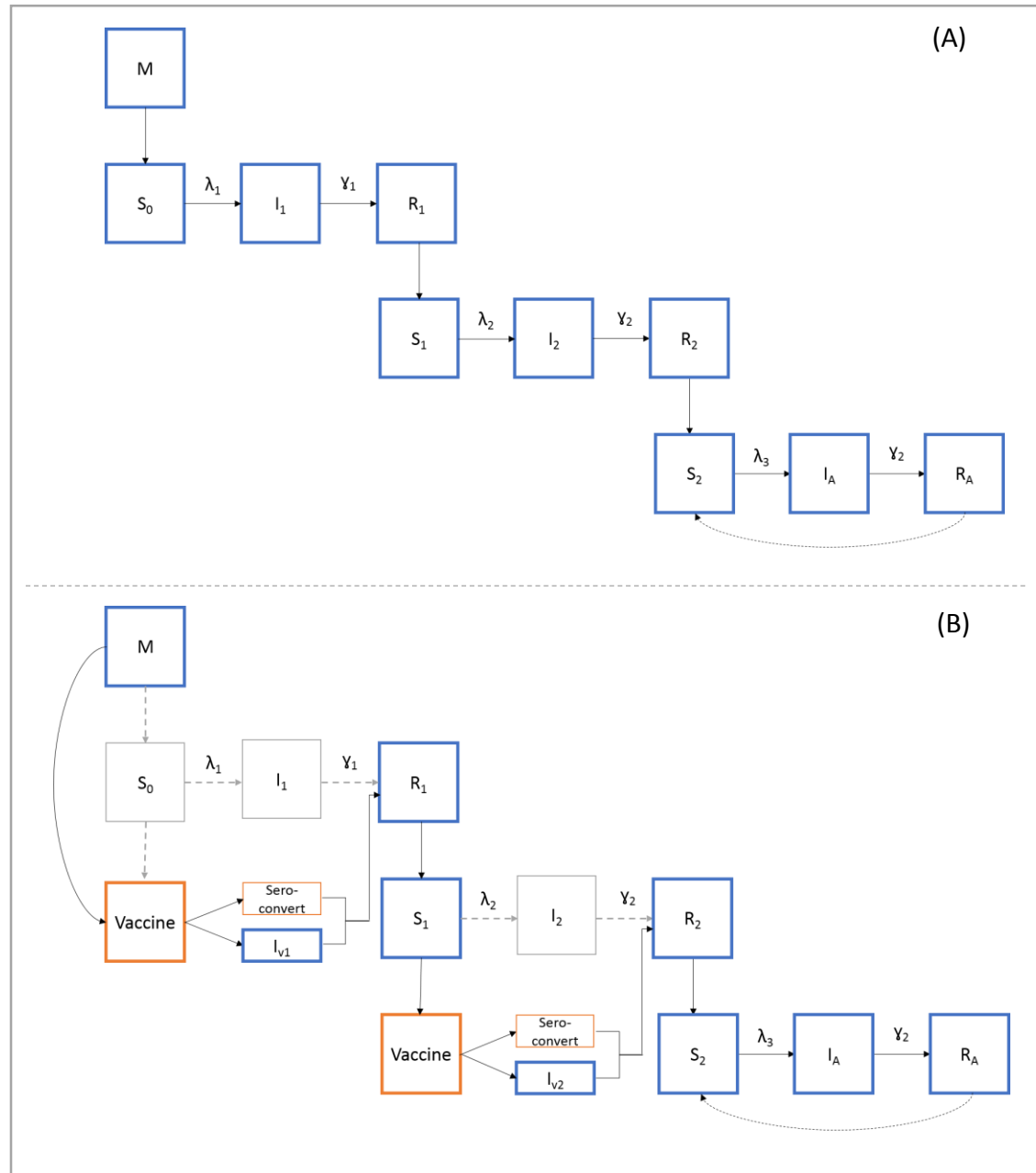


Figure 1. Model structure. (A) Shows the original model structure and (B) shows how vaccination was included in the model. After vaccination a fraction of individuals will not seroconvert, get infected and enter the Infection compartments, I_{v1} or I_{v2} . After some time they will recover from infection and transition into the

respective Recovered compartment, R_1 or R_2 . Vaccinated individuals who seroconvert will not get infected and transition directly into the respective recovered compartment.

Incremental Cost Effectiveness Excel model inputs

Model inputs included vaccine price, administration cost per dose, cost per hospitalization, cost per outpatient visit, and simulated number of rotavirus episodes, outpatient visits, hospitalizations and deaths. As mentioned above, the dynamic model was fitted to health burden estimates for 2015 in order to output health burden estimates (number of episodes, outpatient visits, hospitalizations and deaths) under vaccination and no vaccination for 2015 to 2024. These estimates are the ones that were used in the Excel model.

Health care costs due to rotavirus infection. Only direct medical costs of rotavirus infection were included in the cost effectiveness analysis. Costs were estimated as *cost per outpatient visit* and *cost per hospitalization*. These cost categories include the cost of diagnosis, treatment/drugs, personnel, and facilities. Estimates for the inpatient cost and outpatient cost, excluding drug and diagnostic costs, were obtained using WHO's *Choosing Interventions that are Cost Effective* project (WHO-CHOICE), which provides estimates of the cost per hospital bed day and cost per outpatient visit specific for each country in the project (World Health Organization, 2008). The *cost per hospital bed day* and *cost per outpatient visit* are reported according to facility level; for example, cost per hospital day is reported for primary-level hospitals, secondary-level hospitals and teaching hospitals. We calculated the mean outpatient and hospitalization cost per day by taking an average of the highest and lowest reported cost across facility levels. The cost of treatment and diagnostic tests was calculated as a proportion of hospitalization and outpatient visit costs. Drugs and diagnostic test costs were considered to be an additional 33% of the hospitalization cost and 66% of the outpatient cost (Atherly et al., 2009; Rheingans et al., 2009; Rheingans, Constenla, Antil, Innis, & Breuer, 2007a, 2007c). We assumed the duration of hospitalization due to rotavirus was on average 4 days (Atherly et al., 2009). No additional healthcare costs were included for patients whose infection resulted in death, to avoid double counting. The dynamic model assumes that deaths are a fraction of all hospitalizations; healthcare costs for those infections that result in death are already accounted for within the hospitalization group. Finally, since the analysis was conducted from the perspective of the health system, we did not take into account any external resource use such as time costs, productivity losses, or costs of care of patients who did not present to a clinic or hospital.

Table 4. Input variables for the Excel model: healthcare costs of rotavirus infection in Bangladesh

Variable	Best estimate (range), US\$	Distribution	Reference(s)
Outpatient visit	1.86 (0.93-2.80)	Triangular	(Atherly et al., 2009; Rheingans et al., 2009; Rheingans et al., 2007a; World Health Organization, 2008)
Hospitalization	20.55 (10.28-30.83)	Triangular	(Atherly et al., 2009; Rheingans et al., 2009; Rheingans et al., 2007a; World Health Organization, 2008)
Deaths	None	-	Authors' assumption
Vaccine cost per dose	7.50 (1.00, 7.50)	-	(Madsen, Ustrup, Fischer, Bygbjerg, & Konradsen, 2012; Tate et al., 2014)

Note. The range for the triangular distributions are the upper and lower bound and correspond to $\pm 50\%$.

Costs of introducing rotavirus vaccine in Bangladesh's National Immunization Program. To estimate the cost of adding rotavirus vaccine to the National Immunization Program, we followed WHO's guidelines for estimating costs for new vaccines (World Health Organization, 2002). Although costs were not measured directly (as recommended by WHO guidelines), estimates were obtained from data published by Bangladesh's Government (Government of People's Republic of Bangladesh, 2011). Bangladesh's Comprehensive Multi-Year Plan of the National Immunization Program includes predictions of capital administrative costs the government would likely incur for the introduction of pneumococcal vaccine. We assumed that the administrative and capital costs associated with the introduction of any new vaccine would be comparable, with the exception of costs associated with cold chain expansion. The administrative costs of introducing pneumococcal vaccine included the cost of training materials, social mobilization, surveillance and purchasing of vehicles (Government of People's Republic of Bangladesh, 2011). We assumed these administrative capital costs would be incurred every ten years since personnel need to be periodically retrained and training materials and surveillance methods must be updated over time. In addition to these costs, the Comprehensive Multi-Year Plan mentioned the increase in cold chain equipment needed for the introduction of rotavirus vaccine specifically (Government of People's Republic of Bangladesh, 2011). Cold chain equipment capital costs were estimated using this data, and amortized over eight years, after which time we assumed equipment would need to be replaced. To obtain the administration cost per dose of vaccine, we divided the aggregate vaccine administration cost during ten years (2015 to 2024) by the total number of vaccines procured during that same period (see Table 5).

Table 5. Administration Costs of rotavirus vaccine introduction in Bangladesh's National Immunization Program and administration cost per dose

Cost Category	Estimate	% of total cost
Annual Administration Costs		
<i>Total Recurrent Costs (\$)^{a,b}</i>	772,782	27.2
Cold chain storage operation and maintenance	772,782	27.2
<i>Total Capital Costs (\$)^c</i>	2,069,902	72.8
Vehicles	6,133	0.22
Cold Chain Equipment	1,931,955	68.0
Training materials	124,197	4.37
Social mobilization	6,513	0.23
Surveillance	1,104	0.04
<i>Total Annual Administration Costs (\$)</i>	2,842,684	100
Administration cost per dose		
Total costs over ten years (\$)	28,426,843	
Doses procured in ten years ^d	79,902,667	
Administration cost per dose (\$)	0.36	

Note. All costs are expressed in 2014 US\$. ^aWe assumed that there would be no cost increase in the following recurrent costs suggested by WHO: syringes, safety boxes, waste management, surveillance, transport operation and maintenance. ^bThe cost of vaccines was not included in the administrative cost per dose; the cost of each vaccine dose was added into the excel model as a separate cost. ^cWe assumed that there would be no increase in costs for the following capital cost categories: incinerators and redesign of stationery. ^dThe number of vaccine doses per year was an output of the transmission dynamic model; we assumed a vaccine wastage rate of 10% and

a reserve stock of an additional 25% of vaccine doses only for the first year of vaccine introduction (2015). Source: (Government of People's Republic of Bangladesh, 2011; World Health Organization, 2002)

Vaccine cost was assumed to be \$7.50 per dose for the base case analysis. We assumed there would be 10% vaccine wastage and that the first year the government would purchase an additional 25% of vaccine doses to have as a reserve stock (World Health Organization, 2002).

Cost effectiveness analysis

We investigated the incremental cost effectiveness of rotavirus vaccination and no vaccination from the healthcare system perspective. The primary outcome measure was cost per DALY averted. All estimates are expressed in 2014 US dollars. Health outcomes (episodes, outpatient visits, hospitalizations and deaths) for children under five were obtained from the transmission dynamic model for the years 2015 to 2024 under two scenarios, no vaccination, and vaccination at 92% coverage. The average duration of disease for DALY calculations was assumed to be 6 days (Atherly et al., 2009). When calculating DALYs we assumed that: a rotavirus episode that did not result in care would have a disability weight of mild diarrhea (0.061); an outpatient visit patient would have a disability weight corresponding to moderate diarrhea (0.202); and a hospitalization patient would have a disability weight corresponding to severe diarrhea (0.281) as calculated by (Salomon et al., 2012). To calculate Years of Life Lost (YLL), we assumed a life expectancy of 72.4 years for deaths between 2015 and 2019 and a life expectancy of 74 years for deaths between 2020 and 2024 (Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, 2012). The difference in health outcomes from both scenarios was attributed to vaccination and includes the effect of herd immunity in the reduction of rotavirus' health burden. Following WHO's suggestions on how to evaluate cost effectiveness, we considered vaccination to be *very cost effective* if the cost per DALY averted was lower than the GDP per capita of the nation in which it was implemented and *cost effective* if the cost per DALY averted was below three times the GDP per capita (World Health Organization, 2001). The per capita GDP for Bangladesh in 2013 was US\$958 and was used to assess study results (The World Bank Group, 2015).

Secondary outcomes measured were number of deaths averted, hospitalizations averted, outpatient visits averted, and health care costs averted.

Deterministic Sensitivity Analysis

We conducted a series of one-way sensitivity analyses to see how individual variables would affect the cost effectiveness outcome measure. These analyses were done by changing one parameter at a time and holding all other parameters constant at the base estimates. Variables used in this analysis were vaccine price, administration cost per dose, vaccine efficacy, vaccine coverage, number of rotavirus episodes, outpatient visits, hospitalizations, and deaths (from simulation). For the vaccine price we looked at a reduced costs of \$1.00 per dose and \$2.50 per dose. We choose \$1.00 because Rotavac (Bharat Biotech) is likely to be sold at this price, and \$2.50 the reduced price to which GlaxoSmithKline has committed for the Rotarix vaccine (Madsen et al., 2012).

A two-way deterministic sensitivity analysis was also done to see how changes in two parameters at the same time would affect the incremental cost effectiveness ratio. We used changes in vaccine price in combination with changes in vaccine efficacy.

RESULTS

Dynamic model fitting

Table 6 shows the parameters estimated from fitting the model to data on age-specific rotavirus hospitalizations at the *icddr,b* hospital in Dhaka, and parameters estimated from scaling and fitting the model to rotavirus healthcare burden estimates for Bangladesh.

Table 6. Model parameter values: estimates obtained from fitting model

Estimates from fitting model	Parameter
Estimates from fitting (1) to Dhaka Hospital	
Basic reproduction number (R_0)	31.7
Duration of Immunity ($1/\omega$)	4.6 weeks
Proportion of subsequent infections leading to severe RVGE	0.00023
Estimated from fitting (2)	
Mild cases reporting fraction	Parameter Median (95% CI)
Outpatient visits reporting fraction	0.3437 (0.2383, 0.4611)
Hospitalizations reporting fractions	0.2937 (0.1931, 0.4445)
Deaths reporting fractions	0.4639 (0.3011, 0.7026)
	0.0422 (0.0276, 0.0672)

According to the first fitting, one individual with rotavirus infected 31.7 other individuals (in a completely susceptible population). The fitting also estimated that infected individuals would develop incomplete immunity for 4.6 weeks. Finally, the proportion of subsequent infections leading to severe RVGE was estimated to be 0.00023. The second fitting estimated that out of all rotavirus cases predicted by the model 34.37% would be mild cases, and out of these mild cases 29.37% would be outpatient visits. The fitting also estimated that 46.39% of severe RVGE cases would be hospitalized and out of those 4.22% would die.

Rotavirus health burden and vaccine impact

For Bangladesh in the period 2015 to 2024, we estimated that rotavirus would cause ~109,000 deaths, 2.6 million hospitalizations and 9.3 million outpatient visits in children <5 years of age. Vaccination, at 92% coverage, would reduce mortality by 45% to a total of ~60,100 deaths.

Table 7. Deaths due to rotavirus infection by age, for the two simulated scenarios, 2015 to 2024

Age group	No vaccine scenario	% of total	Vaccine scenario	% of total
<3 months	4,188	4	4,466	7
3 to 12 months	68,327	63	36,449	61
12 to 24 months	26,809	25	13,547	23
24 to 36 months	7,123	7	3,964	7
36 to 48 months	1,908	2	1,181	2
48 to 60 months	672	1	451	1
Total	109,027	100	60,058	100

Table 7 shows deaths broken down by age; the highest mortality was predicted in children between 3 and 12 months, where more than half of all deaths were projected. The number of deaths in children 12

to 24 months was also high, representing approximately one fourth of total deaths. Deaths in the under <3 months of age group is low, as expected, because maternal immunity can provide protection against rotavirus infection (Pitzer et al., 2012). With vaccine introduction hospitalizations and outpatient visits, like deaths, would also decrease by 45% and 36% respectively.

Direct medical costs of rotavirus disease without vaccine introduction were estimated to be ~\$61.8 million. These include the cost of hospitalization due to severe RVGE, which accounted for 75% of costs, and the cost of outpatient visits due to mild RVGE, which accounted for 25% of costs. With vaccine introduction, medical costs would decrease by 42%, to a total of \$36 million. The cost of vaccine administration during the study period was ~\$24.9 million and costs of vaccine procurement, with a vaccine cost per dose of \$7.50, was ~\$525.4 million. This translates to a total cost of \$550 million over 10 years for the vaccination program, and a cost per child vaccinated of \$15.61.

Table 8. Summary of Costs for the two simulated scenarios, from 2015 to 2024

Cost category^b	Cost (million US\$)	Percentage (%)
Medical costs without vaccination		
Outpatient visits	15.2	25
Hospitalizations	46.5	75
Total medical costs ^a	61.8	100
Medical costs with vaccination		
Outpatient visits	9.96	28
Hospitalizations	26.1	72
Total medical costs	36.0	100
Vaccination costs		
Administration cost	24.9	5
Vaccine cost	525.4	95
Total vaccination cost	550.3	100

^bAll costs are discounted at a 3% discount rate to 2015 ^aOutpatient visit and hospitalization costs do not add up to the total medical cost due to rounding.

Incremental cost effectiveness

Vaccination, according to our model, would prevent 10.2 million DALYs. Moreover, the net additional cost of vaccinating would be ~\$524 million. If predicted estimates are correct vaccination would be very cost effective from the healthcare system perspective, at a cost of \$51.19 per DALY averted.

Table 9. Projected impact and incremental cost effectiveness of rotavirus vaccination in Bangladesh, from 2015 to 2024

Variable			
Total Impact	No Vaccination	Vaccination	Averted^b
Total DALYs	26,900,000	16,700,000	10,200,000
Total deaths	109,000	60,100	49,000
Medical costs (\$)	61,800,000	36,000,000	25,700,000
Vaccination costs (\$)	-	550,000,000	-
Incremental Cost-Effectiveness	Estimate (US\$)		
Cost/DALY averted (\$)	51.19		

^bAverted numbers may not add up due to rounding

Sensitivity Analysis

The effect of individual variables on the ICER is shown in Table 10. The two variables that had the greatest effect on the ICER were vaccine price and the estimated number of rotavirus episodes pre-vaccination, which determined our estimate of the reporting fraction of mild RVGE cases and therefore the number of episodes predicted over the 10-year simulation. Unlike these parameters, variation in vaccine coverage, administration cost per dose, cost per hospitalization and cost per outpatient visits had a small effect of less than \$3 per DALY averted.

At a vaccine price of \$1.00 per dose, the ICER would be as low as \$6.80 per DALY averted. At a cost of \$2.50 per dose, vaccination would still be very cost effective with an ICER of \$17.00 per DALY averted. We analyzed the effect of our pre-fitting estimates of number of episodes, number of outpatient visits, number of hospitalizations and deaths on the ICER by changing the corresponding reporting fractions to the lower or upper 95% confidence interval, one at a time. When we did this, the estimate of number of rotavirus episodes had the greatest effect on the ICER. With the lower 95% confidence interval selected the number of rotavirus episodes predicted for the non-vaccination scenario decreased to 10.00 million. Due to this decrease, vaccination had a smaller impact on DALY's averted (6.723 million compared to 10.25 million) which lead to an increase in the ICER to a value of \$78.00 per DALY averted. The opposite occurred when we evaluated the effect of the upper 95% confidence interval. This time the number of episodes increased, which led to a greater number of DALY's averted due to vaccination (11.45 million) and a lower cost per DALY averted of \$45.80. Because we assumed there would be no economic costs for rotavirus episodes that did not seek care, changing the number of episodes had no effect over costs.

Table 10. One-way sensitivity analysis: effect of lower and upper variable estimates on the cost effectiveness ratio, health outcomes and economic burden

Parameter	Variable (range)		Cost Effectiveness		DALYs averted (million)		Cost difference (million) ^a	
	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
Vaccine Efficacy	41	64	58.40	45.30	9.039	11.49	528.0	521.1
Vaccine Coverage	80	100	50.30	51.80	9.070	11.02	455.8	570.4
Episodes ^b	10.00	30.59	78.00	45.80	6.723	11.45	524.6	524.6
Outpatient visits ^b	6.133	14.12	55.80	45.50	9.428	11.48	526.4	521.9
Hospitalization ^b	1.677	3.912	54.30	47.10	9.788	10.92	531.8	514.1
Deaths ^b	0.0713	0.1753	57.00	43.60	9.204	12.03	524.6	524.6
Cost per hospitalization	10.3	30.8	52.20	50.20	10.25	10.25	534.8	514.4
Cost per outpatient visit	0.93	2.8	51.40	50.90	10.25	10.25	527.2	521.9
Vaccine admin. cost per dose	0.18	0.53	50.00	52.40	10.25	10.25	512.3	537.5
Vaccine price per dose 1	2.50	7.50 ^c	17.00	51.19	10.25	10.25	174.3	524.6
Vaccine price per dose 2	1.00	7.50 ^c	6.80	51.19	10.25	10.25	69.3	524.6

^a The cost difference corresponds to all additional costs incurred under the vaccination scenario when compared to the no vaccine scenario. This cost was calculated as (Total medical costs + total vaccination costs)_{vaccination} – (Total medical costs)_{no vaccination}.

^b Total number of episodes, outpatient visits, hospitalizations and deaths, in millions, over the ten year simulation period for the non-vaccine scenario. Lower and upper bound correspond to the 95% Confidence Intervals.

^c Based on (Government of People's Republic of Bangladesh, 2011) we believe vaccine price in Bangladesh could vary from \$7.50 to \$1.00. The be conservative in our analysis we set our base case as the upper bound.

Figure 2 displays a summary of the one-way sensitivity analysis; if estimates of the healthcare burden of disease (number of episodes, outpatient visits, hospitalizations and deaths) and vaccine efficacy were overestimated, reducing these parameters to the real value would have the heaviest negative impact on the ICER, and result in an increased cost per DALY averted. Nonetheless, changes in these parameters to a lower value, did not drive the intervention above the very cost effective threshold of three times the country's GDP (World Health Organization, 2001); this shows the robustness of our conclusion that vaccination is very cost-effective. On the other hand, if these estimates were below real values, increasing them would result in a more cost effective intervention with a lower cost per DALY averted.

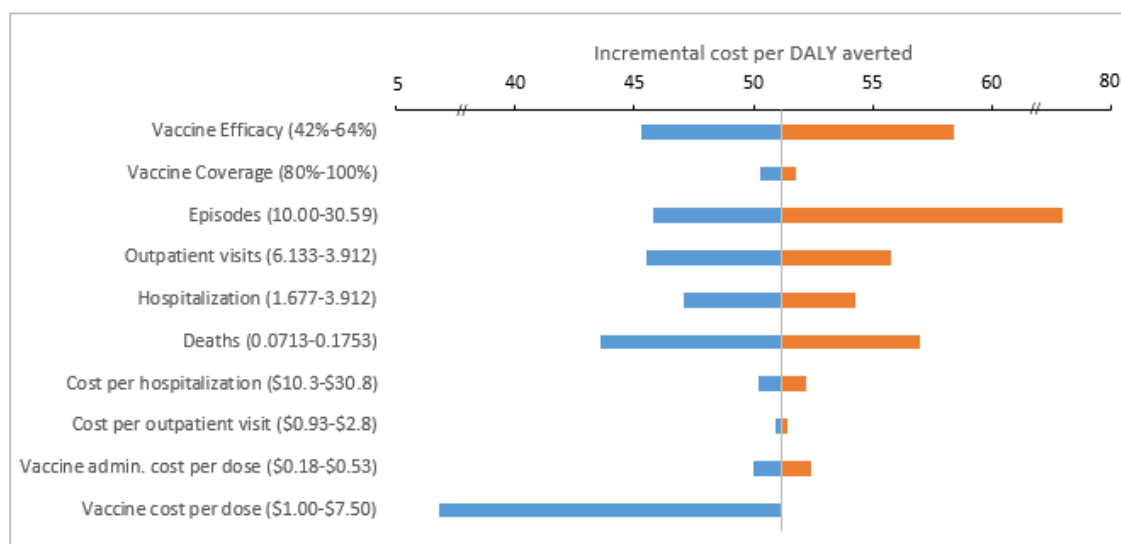


Figure 2. One-way sensitivity analyses on lower and upper bound estimates of model variables. Episodes, Outpatient visits, Hospitalizations and Death are 95% CI and are reported in millions. Costs are $\pm 50\%$.

Figure 3 shows the impact of simultaneous changes in price and vaccine efficacy on the cost effectiveness estimate. As vaccine efficacy increases and price per dose decreases vaccination becomes more cost effective and the cost per DALY averted can be as low as \$5.72. On the other hand, as price increases and vaccine efficacy decreases the cost per DALY averted rises, and can be as high as \$58.42.

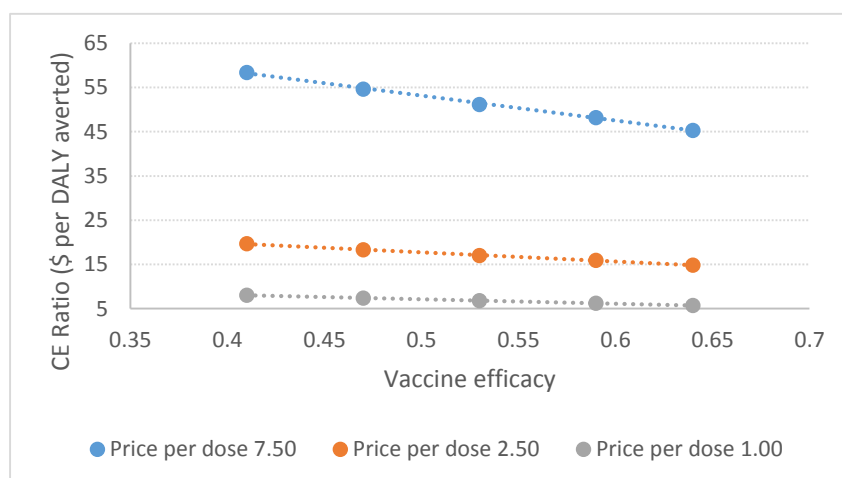


Figure 3. Two way sensitivity analysis of the effect of vaccination efficacy and price per dose on the cost effectiveness of rotavirus vaccine introduction in Bangladesh.

DISCUSSION

In Bangladesh, Rotavirus disease is estimated to cause approximately 9,857 deaths and 246,000 hospitalizations per year, which imposes a great burden on this country's healthcare system (Tate et al., 2012; Zaman et al., 2009). In order to evaluate the impact of vaccination on reducing the burden, we conducted an incremental cost-effectiveness analysis comparing vaccination and no vaccination during a ten-year period. We then obtained information on the potential cost per DALY averted resulting from introduction of rotavirus vaccine through Bangladesh's National Immunization Program. This, we hope, will help inform the decision of whether to introduce rotavirus vaccination in the country.

We estimated the health sector in Bangladesh will spend approximately \$62 million treating RVGE cases over the next ten years. Three quarters of the estimated costs were attributable to RVGE hospitalizations. For this reason, interventions that prevent or reduce the rate of hospitalization would decrease rotavirus associated medical costs substantially, and should thus be considered. For example, simulating vaccination at current DTP3 coverage levels resulted in a 42% reduction of direct RVGE medical costs and translated into savings of \$25.7 million. Still, even when considering medical costs averted, vaccination would represent a large investment for Bangladesh. At a cost per dose of \$7.50, the government would need to spend ~\$55 million per year to introduce and deliver the vaccine. This cost is substantial and would be equivalent to ~28% of the public health expenditure by the government (~\$1.9 billion per year in 2013) (The World Bank Group, 2015). This budget concern becomes even more evident when comparing the per child cost of vaccination of \$15.60 with the average health expenditure per capita in the country of \$31.60 (2013) (The World Bank Group, 2015). In order to carry out this intervention, Bangladesh's government would need financial support from organizations such as GAVI. GAVI has already supported introduction of rotavirus vaccine in 19 countries and plans to expand its funding to 30 countries by 2015 (GAVI the vaccine alliance, 2015g). With a GNI per capita of \$1,101 (2014) Bangladesh, as of 2015, is eligible for co-financing (GAVI the vaccine alliance, 2015c; The World Bank Group, 2015). Having said this, Bangladesh has limited resources for healthcare spending and competing priorities, such as the recent introduction of pneumococcal vaccine (GAVI the vaccine alliance, 2015a). Although our study examines the comparative value (cost per DALY averted) of vaccination and shows its worth, it does not address the question of who could pay for this intervention, who would benefit from it, and who might lose. Conducting further analyses to address these questions would be beneficial.

Immunization would also significantly reduce morbidity and mortality caused by rotavirus infection. Vaccination from 2015 to 2024 could save ~49 million lives in children under five, which would directly contribute to WHO's fourth millennium development goal of reducing child mortality by two thirds. More than 75% of the deaths predicted by the model occurred in children 3 to 24 months old, which is consistent with literature showing that the greatest number of diarrhea hospitalizations occurs in children under two, and validates model predictions (John et al., 2014; Zaman et al., 2009). Furthermore, simulated vaccination at 92% coverage prevented 45% of hospitalizations and 36% of outpatient visits. The difference in hospitalization and outpatient visit reductions was due to the fact that the model assumed vaccination produced slightly stronger protection against severe RVGE compared to mild RVGE, and we assumed only severe RVGE cases were hospitalized, whereas any RVGE could lead to an outpatient visit.

Introducing rotavirus vaccine into Bangladesh's National Immunization Program is an attractive option that would help decrease the healthcare and economic burden caused by RVGE. Moreover, vaccination would be very cost effective at a low price of \$51.19 per DALY averted, much lower than Bangladesh's GDP per capita of \$958 in 2013. At this very cost effective ICER vaccination should be implemented (World Health Organization, 2001).

Our analysis shows that if the Rotavac vaccine were to provide protection similar to that assumed by our model and was offered at \$1 per dose, the cost per DALY saved would be as low as \$6.80. It is reasonable to think that cost of vaccines will be driven down by the entrance into the market of new players (such as Rotavac) and that vaccination will become more cost effective with time. Our one-way sensitivity analyses show that cost per DALY saved could vary from \$6.80 to \$78.00. This makes us confident that vaccination is cost-effective, given that the worst estimate is still very cost-effective by international standards. Having said this, changes in multiple parameters at the same time might negatively affect the ICER, and needs to be evaluated. Variables that had the greatest impact on the cost effectiveness estimate were vaccine efficacy, number of episodes, outpatient visits, hospitalizations and deaths. Additional information on the current healthcare burden of rotavirus and vaccine efficacy in Bangladesh would be instrumental in developing more accurate cost effectiveness estimates.

Our findings have important limitations that could impact the estimated cost effectiveness and should be delved into at greater depth in the future. The first limitation is that our estimates of disease burden (number of episodes, outpatient visits, hospitalizations and deaths) were partially based on data from a cohort of children in India, which might not reflect the burden of disease in Bangladesh. Furthermore, we adapted a transmission model of rotavirus infection developed for high socioeconomic settings such as those found in the United States (Pitzer et al., 2009). Some of the assumptions included in the model might not be the same for developed and developing nations, and need to be further adapted to reflect rotavirus transmission in low socioeconomic settings. Our model assumed that vaccination would reach a coverage level of 92% from the start and that all children would receive a full course of two doses. This is unlikely, as vaccination coverage at the beginning will probably be below that of DTP3, and benefits of vaccination in initial years after implementation might be below those predicted. Moreover, we only considered what would happen in children under five, where most of the burden of rotavirus occurs, prior to vaccine introduction. However, it has been suggested that vaccination increases the age of first infection and could shift the burden of infection to older children (Pitzer et al., 2012; Pitzer et al., 2009). We may have overestimated the health benefits of vaccination by not taking into account an increase in RVGE in persons above five years of age in the model. Obtaining primary cost data on hospitalization, outpatient visits, diagnosis and treatment of rotavirus in Bangladesh would be helpful in valuing the economic burden of this disease. Finally, undertaking a probabilistic uncertainty analysis would have better described the possible range of incremental cost effectiveness values for the introduction of rotavirus vaccination in Bangladesh, and is the next step in our study.

Cost-effectiveness analyses provide a valuable tool to compare different health programs and look at the effect of specific interventions in improving the quality of life of the targeted population. Rotavirus morbidity and mortality in Bangladesh is substantial, and our study indicates that vaccinating against rotavirus would greatly reduce the burden caused by this disease while being very cost effective at a low cost per DALY averted of \$51.19. This cost-effectiveness analysis can be useful to compare the cost and benefits of rotavirus immunization against other competing health care and development priorities (interventions?), and in this way help allocate funds efficiently (effectively?). Moreover, study findings

can be used by the Bangladeshi government to advocate for vaccine introduction, and build a case for vaccination when seeking external funding and co-financing support.

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